VERMONT

Office of Vermont Health Access

Therapeutic Class Review
Long-Acting Narcotics

Overview/Summary

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1] It is a subjective experience that is difficult to identify or quantify by any observer and is unique to the individual. The type of pain that one may experience is often described by its pathophysiological source. Somatic pain is due to activation of pain receptors in cutaneous or deep tissues. This type of pain is usually well localized and is described as sharp in nature. Visceral pain involves internal areas of the body, may be poorly localized, and described as an ache. Neuropathic pain is generally described as burning or electrical in nature. This type of pain is due to neuronal injury and may have a corresponding neurological deficit.[2] Understanding the type of pain and its source will play a role in choosing pain management therapies.

Successful pain management can be a difficult goal to attain. An individual's reaction to pain and response to pain management can be highly variable. Pain thresholds vary greatly between patients and responses to therapy will vary between persons and may vary within the same patient from day to day. Pain management can be multifaceted and may incorporate both pharmacological and non-pharmacological therapies. Successful pain management may require frequent reassessment of pain level and response to therapy with adjustments made accordingly.

Opioids have been a mainstay in the treatment of moderate to severe pain associated with a number of etiologies and opioids are commonly used in the postoperative and malignant pain settings. Although the routine use of opioids in nonmalignant pain is controversial, opioids are an acceptable alternative to other analgesic interventions that have been ineffective.[2]

Opioids produce their pharmacologic and adverse effects through binding to opioid receptors throughout the central nervous system and peripheral tissues. These agents may be classified by their ability to stimulate or block three types of opioid receptors: mu, kappa, and delta. The mu receptor is considered the prototypical opioid receptor. When stimulated, the mu receptor produces analgesia, euphoria, reduced gastrointestinal motility, respiratory depression, sedation, nausea, tolerance, and physical dependence. Kappa receptor stimulation produces analgesia, dysphoria, psychotomimetic effects, miosis, and respiratory depression. Stimulation of the delta opioid receptor produces analgesia without respiratory depression.[2]

Opioids may be administered via many routes. The general consensus is to use the least invasive, most cost-effective method of delivery before moving on to more invasive administrative techniques. Unlike other analgesic classes, opioids have well-accepted equianalgesic doses, which allows clinicians to convert between agents and between routes of administration. Additionally, pure opioid agonists do not have a ceiling effect as other analgesics do, therefore, additional analgesia may be obtained by increasing the opioid dose. Close monitoring after an opioid conversion or dosage change is required to evaluate the need for further dosage adjustments.[2]

In patients that experience chronic pain, it is recommended that once a stable short acting (immediate release) opioid dose is reached, the patient then be converted to a long-acting agent.[2] The long-acting opioid should be used on a scheduled basis, with as needed short-acting medications prescribed for breakthrough pain. The as needed dose should be approximately 15% to 50% of the total daily scheduled

medication dose.[2] Patients who routinely require frequent breakthrough doses within a dosing interval may benefit from an increase in their scheduled medication. The goal is to maintain a constant level of pain relief with the scheduled medication, while only occasionally requiring the breakthrough medication.

Opioids are classified as controlled substances by the Food and Drug Administration (FDA) due to their known potential for abuse. However, it is important to recognize that tolerance and physical dependence are potential and common physiologic changes that occur in most patients who receive opioids for a sustained amount of time. Tolerance is defined as the need for increased dosage to produce the same effect or a reduced effect is observed with a constant dose. Physical dependence occurs when the body becomes accustomed to receiving opioids due to neuroadaption.[3] If the opioids are stopped or decreased abruptly, or if an antagonist is administered, the body will exhibit withdrawal symptoms. To avoid opioid withdrawal, the dose of opioids should be slowly tapered (25% reduction in dose every other day) upon drug discontinuation.[2] Psychological dependence, or addiction, indicates that the patient is taking the medication for reasons for their psychic effects and is characterized by compulsive use despite harm. This occurrence is not a characteristic of the drug class alone, but is a combined effect of biochemical, societal, and psychological factors affecting the patient.[3]

This review encompasses those agents referred to as long acting narcotics (opioid agonists). Short-acting narcotics, agonist-antagonist agents, and other therapeutic options for treating pain are covered in reviews found elsewhere. Agents included in this review are FDA scheduled II and are self-administered.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Fentanyl (Duragesic®)	Opioid agonist	✔
Methadone (Dolopine®, Methadose®)	Opioid agonist	✔
Morphine sulfate controlled release (MS Contin®)	Opioid agonist	✔
Morphine sulfate extended release (Avinza®, Kadian®)	Opioid agonist	-
Morphine sulfate sustained release (Oramorph SR®, Roxanol SR®)	Opioid agonist	✔
Oxycodone controlled release (Oxycontin®)	Opioid agonist	✔ *
Oxymorphone (Opana® ER)	Opioid agonist	-

* Generic availability is sporadic and does not include all strengths.

Indications

Overall, long acting narcotic medications are effective when treatment of moderate-severe pain is required for an extended period of time. The specific Food and Drug Administration-approved indications are summarized below in Table 2.

Table 2. Food and Drug Administration Approved Indications[4-12]

Generic Name	Indications
Fentanyl	Management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate release opioids
Methadone	Treatment of moderate to severe pain not responsive to non-narcotic analgesics Detoxification treatment of opioid addiction Maintenance treatment of opioid addiction, in conjunction with appropriate social and medical services
Morphine sulfate	Management of moderate to severe pain when a continuous, around-the-clock

Generic Name	Indications
controlled release	opioid analgesic is needed for an extended period of time
Morphine sulfate extended release	Relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time
Morphine sulfate sustained release	Relief of pain in patients who require opioid analgesics for more than a few days
Oxycodone controlled release	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Oxymorphone	Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time

Pharmacokinetics

Table 3. Pharmacokinetics[4-12]

Generic Name (Trade name)	Bioavailability (%)	Onset	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Fentanyl	Unknown	12-24 hours	75 as metabolites and 10 as unchanged drug	None	17
Methadone	36-100	2 hours	21 as unchanged drug	No	Highly variable; 8-59
Morphine sulfate	20-40	Not reported	2-12 as unchanged drug	Yes	Controlled Release: 1.5-4.5 Sustained Release: 15
Oxycodone controlled release	60-87	1 hour	19 unchanged, conjugated oxycodone up to 50, 14 conjugated oxymorphone	Yes (noroxycodone, oxymorphone)	4.5-8.0
Oxymorphone	10	Not reported	<1 of the administered dose is excreted unchanged in the urine	Activity of oxymorphone-3-glucuronide; activity of 6-OH-oxymorphone has shown in animal studies to have analgesic bioactivity	Not reported

Clinical Trials

Long acting narcotics have been studied in a number of clinical trials to evaluate and compare analgesic effects in the treatment of pain. A search for clinical trials evaluating the use of these agents in the treatment of various pains resulted in a substantial number of published articles.

Overall, opioid therapy is an effective treatment for patients suffering from moderate to severe pain.[13] Systematic reviews have demonstrated that opioids reduce pain and improve functional outcomes better than placebo.[14] The majority of the studies included in this review are comparative studies with two long-acting narcotics. Placebo controlled trials are rarely used due to the severity and chronic nature of the pain. Cross over designs are being used with increasing frequency in the evaluation of opioid analgesics in cancer pain to compare different opioids, different formulations of the same opioid, and different routes of administration. The studies included in this review include patients that experienced a variety of chronic pain conditions including cancer pain, osteoarthritis, and chronic back pain.

Table 4. Clinical Trials[15-27]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Langford et al[15] TDF patch 25-100 µg/hour every 72 hours vs placebo	MC, PC, RCT Patients (at least 40 years of age) meeting the ACR diagnostic criteria for hip or knee OA and requiring joint replacement surgery, with moderate to severe pain that was not adequately controlled with weak opioids	N=399 6 weeks	Primary: Pain relief, expressed as the difference in the average AUC of the VAS scores over time between baseline and study end Secondary: Function, assessed by the WOMAC score, and individual aspects of pain relief affecting mobility and quality of life	Primary: TDF was associated with significantly better pain relief than that with the placebo patch; the primary end point of the $AUCMB_{avg}$ was -20.0±1.4 (mean±SEM) for patients receiving TDF and -14.6±1.4 for patients receiving placebo (*P*=0.007). Secondary: The mean±SD VAS score for morning and evening pain in the target joint fell from 73.1±15.3 at baseline to 49.5±26.3 at study end in the TDF group and from 73.3±15.7 to 55.4±26.5 in the placebo group. WOMAC scores for pain, stiffness, and physical function improved significantly from baseline to study end in both groups. However, the overall WOMAC score and the pain score were significantly better in the TDF group, while stiffness and physical functioning scores showed non-significant trends in favor of TDF. Significantly more patients who received TDF than those who received placebo reported that the patches definitely met their overall expectations (28% vs 17%; *P*=0.003). When asked to compare the study medication with previous treatments, significantly more patients who received TDF considered it to provide much better or somewhat better relief than other pain medication (60% of the TDF group vs 35% of the placebo group; *P*<0.001). Not all of the individual domains of the SF-36 quality of life assessment showed significant improvements from baseline, although the physical component scores

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				improved significantly in both groups. Scores on the SF-36 pain index were significantly better for patients receiving TDF (*P*=0.047), whereas changes in the mental component scores showed a small, but statistically significant, benefit in those receiving placebo (1.1±0.7; *P*=0.041).
Finkel et al[16] TDF patch 12.5-100 µg/hour applied every 3 days	MC, OL, SA Patients 2 to 16 years of age with moderate to severe chronic pain due to malignant or nonmalignant disease	N=199 15 days (with 3 month extension)	Primary: Global assessment of pain treatment, degree of pain, level of play and activity, overall quality of life, and safety Secondary: Not reported	Primary: The most common starting dose of TDF was 25 µg/hour, which was required by 90 patients (45.2%). The lowest starting dose, 12.5 µg/hour, was considered appropriate for 59 patients (29.6%). The average duration of treatment with TDF in the primary treatment period was 14.80±0.25 days in the ITT patient group. A total of 84.9% of patients received at least 1 rescue medication, with a mean oral morphine equivalent of 1.35±0.16 mg/kg during the primary treatment period. The average daily pain intensity levels reported by parents/guardians using the numeric pain scale for the ITT population decreased steadily throughout the study period from 3.50±0.23 at baseline to 2.60±0.21 by day 16. Parent/guardian-rated improvements in mean patient satisfaction scale scores were observed from baseline (41.22±1.68) to the data collection endpoint (53.80±1.91). One hundred eighty patients (90.5%) reported at least 1 adverse event during treatment. The most frequent adverse events were fever (n=71 patients), emesis (n=66 patients), nausea (n=42 patients), headache (n=37 patients), and abdominal pain (n=34 patients). Secondary: Not reported
Allan et al[17] Morphine sulfate sustained release for 4 weeks	INT, MC, OL, RCT, XO Patients over 18 years of age with chronic	N=256 8 weeks	Primary: Patient preference, pain control, quality of life, and safety assessment	Primary: Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred TDF to oral sustained release morphine (138 (65%) vs 59 (28%); *P*<0.001). The predominant reason given for preferring fentanyl was better pain relief, followed by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs TDF for 4 weeks	non-cancer pain requiring continuous treatment with potent opioids for six weeks preceding the trial		Secondary: Not reported	greater convenience and fewer adverse events. Patients treated with TDF had an average lower pain intensity scores than those treated with sustained release oral morphine (mean 57.8, range 33.1 to 82.5 vs mean 62.9, range 41.2 to 84.6; *P*<0.001), irrespective of the order of treatment. More patients receiving TDF considered their pain control to be good or very good than those receiving morphine (35% vs 23%; *P*=0.002). In the investigators' opinion, global efficacy of TDF was good or very good in 131 of 225 (58%) patients compared with 75 of 224 (33%) patients receiving morphine (*P*<0.001). The corresponding percentages from the patient assessments were 60% for TDF and 36% for morphine (*P*<0.001). Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (SD) consumption was significantly higher with TDF (29.4 [SD 33.0] mg) than with morphine (23.6 [SD 32.0] mg; *P*<0.001). A significant period effect was also observed: the higher consumption during TDF treatment was more apparent in the second trial period (mean 32.4 [SD 38.5] mg) than the first (26.3 [26.0] mg), where the consumption of the rescue drug remained essentially the same over the two treatment periods in the morphine group (23.7 [SD 35.3] mg vs 23.6 [SD 27.3] mg). Patients receiving TDF had higher overall quality of life scores than patients receiving sustained release oral morphine in each of eight categories measured by the SF-36. Differences were significant in the bodily pain (*P*<0.001), vitality (*P*<0.001), social functioning (*P*=0.002), and mental health (*P*=0.020). The overall incidence of treatment related adverse events was similar in both groups as was the proportion of patients with adverse events (74% vs 70%). TDF was associated with a higher incidence of nausea (26% vs 18%) than was sustained release oral morphine, whereas constipation was less common with TDF than with morphine (16% vs 22%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Agarwal et al[18] TDF patch 25-150 µg/hour every 3 to 4 days	OL, PRO Patients over the age of 18 with neuropathic pain persisting for >3 months	N=53 16 weeks	Primary: Change in pain intensity and daily activity Secondary: Pain relief, cognition (measured by grooved pegboard test), physical function (measured by MPI), mood (measured by BDI), and adverse events	Primary: The average pain reduction across the population using pain diary data was -2.94±0.27. A similar reduction of 3.02±0.22 was obtained using the data from the Actiwatch. Thirty subjects (30/53; 57%) reported >30% improvement in pain and 21 (21/53; 40%) reported >50% change in pain intensity. The decrease in pain scores in the subgroups was: peripheral neuropathy, -3.40±0.44; complex regional pain syndrome-1, 2.40±0.40; and postamputation pain, -2.70±0.47. There was a trend toward a greater reduction in pain intensity in the peripheral neuropathy group compared with the complex regional pain syndrome-1 (*P*=0.06) and postamputation (*P*=0.07) pain states using an ITT analysis. Among completers, TDF was more effective in reducing pain in the peripheral neuropathy subjects compared with the other two groups of patients (*P*<0.04). Overall, 32.5% of patients experienced both a >30.0% decrease in pain intensity and a >30.0% increase in activity. The effect of TDF on activity was that 62% of subjects experienced a >15% increase in activity levels compared with baseline, 20% showed minimal or no change (±15%) in activity, and 18% showed a more than 15% reduction in activity. Secondary: The mean percentage pain relief for the ITT population was 33.7±14.0%, and for subjects who completed the protocol, it was 48.4±15.2%. When the study population was subdivided among the tree groups, the percentage pain relief was greater (*P*<0.01) for subjects with peripheral neuropathy (40.0±15.2%) than for those with complex regional pain syndrome-1 (28.3±11.6%) and postamputation pain (25.9±6.3%). The change in the grooved pegboard test for the whole group for dominant hand was -1.46±5.8 seconds and for the non-dominant hand, it was -5.9±12.2 seconds (not significant). The change in MPI-Interference for the whole group was 0.20±0.94 (not significant), and the change in MPI-Activity was -0.03±0.80 (not significant). The difference in the BDI was 0.03±0.32 (not significant).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Drowsiness (n=25/53; 47.2%) and nausea/vomiting (n=15/53; 28.3%) were common side effects reported by the subjects. A total of 9.4% of the subjects experienced constipation. Five had skin reactions in response to TDF. The severity of side effects decreased during the maintenance period.
Ahmedzai et al[19] TDF for 15 days vs morphine extended release for 15 days	OL, RCT, XO Patients age 18-89 with cancer who required strong opioid analgesia and were receiving a stable dose of morphine for at least 48 hours	N=202 30 days	Primary: Pain control, affect on sedation and sleep, bowel function, treatment preference, and adverse events Secondary: Not reported	Primary: No significant differences on any of the pain scales were detected between the TDF and morphine phases. During the TDF phase, patients used more immediate-release morphine than during the sustained release morphine phase. Rescue medication was used, on average for 53.9% of days during TDF treatment, compared with 41.5% of days for morphine (*P*=0.0005) throughout the whole of the phases. A sizeable proportion of patients required upward titration of study medication (47.1% required at least one TDF dose change and 27.4% at least one morphine dose change). One patient required a downward titration in TDF dose. TDF treatment was associated with significantly less daytime drowsiness than morphine (mean percent AUC, 34.0; 95% CI, 29.1 to 38.9; vs 43.5; 95% CI, 38.5 to 48.5; respectively, as assessed by VAS in the patient diaries). Data from the EORTC questionnaire showed significantly less sleep disturbance with morphine (mean scores, 32.4; 95% CI, 26.9 to 37.9; vs 22.4; 95% CI, 17.8 to 27.1; for TDF and morphine, respectively). The only difference in diary data was that patients reported shorter sleep duration when on TDF compared to morphine over the whole 15-day treatment period (mean, 8.1; 95% CI, 7.9 to 8.3 hours; vs 8.3; 95% CI, 8.0 to 8.5 for morphine). TDF treatment was associated with significantly less constipation than morphine (*P*<0.001). The EORTC quality of life questionnaire revealed no other significant differences between the two treatments. When scores for nausea and vomiting were separated, the mean score for nausea was significantly lower in the TDF group (1.7; 95% CI, 1.5 to 1.8; vs 1.8; 95% CI, 1.7 to 2.0; *P*=0.04). At the end of the trial, significantly more patients indicated that TDF had caused less interruption to their daily activities, and the activities of family and care takers, and had

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				been more convenient to take than the morphine tablets. The percentages expressing preference were as follows: less interruption of daily activities: 55.2% TDF, 20.4% morphine; less interruption to care givers: 49.0% TDF, 22.3% morphine; and more convenient medication: 58.3% TDF, 22.3% morphine. Of the 202 patients who entered the study, 136 felt able to express an opinion about the two treatments. Of these, 14 (10%) had no preference, 73 (54%) preferred TDF, and 49 (36%) preferred the morphine tablets (*P*=0.037). Although more adverse events were reported during TDF treatment, the end of treatment questionnaire indicated that significantly fewer patients considered that TDF caused side effects compared to morphine (40.4% for fentanyl versus 82.5% for morphine; *P*<0.001). Secondary: Not reported
Allan et al[20] TDF 25 µg/hour every 72 hours with titration according to pain levels vs morphine sulfate sustained release 30 mg every 12 hours with titration according to pain levels	MC, OL, PG, RCT Adults with chronic lower back pain requiring regular strong opioid treatment	N=673 13 months	Primary: Compare the pain relief for each treatment as measured by VAS in a patient diary, bowel function assessment Secondary: SF-36 questionnaire, assessment of disease progression, adverse events	Primary: The mean dose of TDF on day 1 was 25 µg/hour (range 25-50 µg/hour) and 57 µg/hour (range 12.5-250.0 µg/hour) at study end. The mean dose of morphine sulfate sustained release on day 1 was 58 mg (range 6-130 mg) and 140 mg (range 6-780 mg) at endpoint. Both treatments afforded similar degrees of pain relief. The mean VAS scores at study endpoint were 56.0±1.5 for TDF and 55.8±1.5 for morphine sulfate sustained release. The 95% confidence interval for difference between groups was -3.9 to 4.2, which fell well within the -10, +10 predefined definition of non-inferiority. Pain relief was evident after 1 week of treatment when mean VAS scores were 58.5±1.3 for TDF and 59.9±1.4 for morphine sulfate sustained release. TDF was associated with significantly less constipation than morphine sulfate sustained release. Baseline levels of constipation were similar but at endpoint 31% of TDF patients (93 of 299) and 48% receiving morphine sulfate sustained release (145 of 298) were constipated (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Mean quality of life scores improved to a similar extent in both treatment groups between baseline and endpoint for all domains of overall physical health (*P*<0.001), physical functioning, role-physical, bodily pain, vitality, social functioning, and role-emotional. However the scores for overall mental health did not change significantly from baseline to endpoint in either group (*P*=0.937 for TDF, *P*=0.061 for morphine sulfate sustained release). Fifty to 70% of patients improved by at least one pain category (e.g., from severe to moderate) during the course of the trial in both groups. While the TDF group improved more than the morphine sulfate sustained release group for pain during the day and pain at rest, the groups improved to a similar degree for pain on movement and pain at night. The dose of supplemental medication for breakthrough pain did not differ significantly between the treatment groups. Most participants (95%) reported at least one adverse event during the study: 87% of patients taking TDF and 91% taking morphine sulfate sustained release reported an adverse event that was considered at least possibly related to the trial mediation. Adverse events led to discontinuation of trial medication in 37% of the TDF group and 31% of the morphine sulfate sustained release group (*P*=0.098). The most common adverse events leading to discontinuation were nausea (37% of discontinuations in each group), vomiting (24% TDF, 20% morphine sulfate sustained release), and constipation (11% TDF, 23% morphine sulfate sustained release). Time to first report of constipation was also significantly longer in the TDF group (107±9 days vs 43±5 days for morphine sulfate sustained release; *P*<0.001). Investigator ratings of disease progression were similar across treatment groups. At endpoint, investigators considered 49% of TDF and 45% of morphine sulfate sustained release patients had stable disease; 10% and 8%, respectively, had deteriorated; and 21% and 23%, respectively, had improved.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sloan et al[21] Oxycodone controlled release vs morphine controlled release	MC, MD, OL, PRO, XO Adults 18-80 years of age with a history of chronic cancer pain requiring at least 20 mg of oxycodone or the analgesic equivalent of at least 30 mg of oral morphine per day	N=63 1 week	Primary: Analgesic effectiveness and safety Secondary: Not reported	Primary: Mean daily pain intensity scores were comparable during each treatment sequence, indicating that pain was stabilized throughout the study. There were no significant changes in the mean VAS scores for quality of life domains or for the mean change in patient recall for the quality of sleep for the treatment groups. There were no statistically significant differences in adverse events. Secondary: Not reported
Kivitz et al[22] Oxymorphone extended release 10 mg every 12 hours vs oxymorphone extended release 40 mg every 12 hours vs oxymorphone extended release 50 mg every 12 hours	DB, DR, MC, PG, RCT Patients age 18 and over that had OA as defined by the presence of typical knee or hip joint symptoms, signs, and radiographic evidence	N=370 2 weeks	Primary: Mean change in arthritis pain intensity Secondary: Change in the pain, stiffness, and physical function subscales of WOMAC OA index and the WOMAC composite index, quality of life measured using SF-36, quality of sleep, and tolerability	Primary: In the ITT population, the least squares mean change in arthritis pain intensity from baseline to the final visit, as measured on the 100-mm VAS, were -21, -28, -29, and -17 mm for oxymorphone extended release 10, 40, 50 mg, and placebo respectively. The least squares mean differences in change from baseline compared with placebo were -4.3 (95% CI, -12.8 to -4.3; *P*=NS), -11.1 (95% CI, -19.7 to -2.5; *P*=0.012), and -12.2 (95% CI, -20.9 to -3.5; *P*=0.006) for the 10, 40, and 50-mg doses of oxymorphone extended release respectively. Compared with placebo, arthritis pain intensity scores were improved by 62.8% and 70.9% after treatment with oxymorphone extended release 40 or 50 mg every 12 hours, respectively (*P*=0.012 and *P*=0.006). Secondary: Overall, improvements in WOMAC scores were 2- to 3-fold greater in oxymorphone extended release recipients than in placebo recipients. From baseline to the final visit, 2-fold greater decreases in WOMAC pain subscale scores were found in all 3 oxymorphone extended release groups compared with the placebo group ($P \leq 0.025$). Improvements in WOMAC physical function subscale scores also were significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				greater for each of the oxymorphone extended release groups compared with the placebo group ($P \leq 0.025$). Improvements in the WOMAC stiffness subscale score were significant compared with placebo for the oxymorphone extended release 40 and 50 mg groups ($P \leq 0.001$) but not for the 10 mg group. With respect to the WOMAC composite index, pairwise comparisons of the placebo group with each of the oxymorphone extended release groups found significantly greater improvements in each oxymorphone extended release group ($P \leq 0.025$). All patients who received oxymorphone extended release, irrespective of the dose, had significant improvements in the SF-36 score compared with placebo. The changes from baseline were 3.9, 4.6, 3.6, and -0.1 points with oxymorphone extended release 10, 40, and 50 mg, and placebo, respectively ($P<0.001$). Improvements in the complete regional pain syndrome score for overall sleep quality were 2-fold greater in patients who received oxymorphone extended release 40 and 50 mg than in the placebo group ($P \leq 0.05$). The change in sleep quality in the oxymorphone extended release 10 mg group was not significant compared with placebo. The most frequently reported adverse event in the oxymorphone extended release groups were nausea (39.4%), vomiting (23.7%), dizziness (22.6%), constipation (22.2%), somnolence (17.6%), pruritus (16.5%), and headache (14.7%).
Bruera et al[23] Methadone 7.5 mg by mouth every 12 hours and 5 mg every 4 hours as needed vs morphine sustained release 15 mg	DB, MC, PG, RCT Patients aged 26-87 that had poor control of pain caused by advanced cancer with a life expectancy of at least 4 weeks	N=103 4 weeks	Primary: The difference in pain intensity Secondary: Toxicity (as calculated as the sum of the following individual symptom items: sedation, nausea,	Primary: The proportion of patients with a 20% or more improvement in pain expression at day 8 was similar for both groups, with 37 of 49 patients (75.5%; 95% CI, 62% to 89%) in the methadone group and 41 of 54 patients (75.9%; 95% CI, 63% to 89%) in the morphine group. Day 29 outcomes showed no significant difference between the methadone group and the morphine group in regards to pain response of 20% or greater and patient-reported global benefit. Secondary: There was no statistically significant difference between treatment groups for the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 12 hours and 5 mg every 4 hours as needed			confusion, and constipation)	parameter of composite toxicity worse by 20% or more
Morley et al[24] Phase 1: Methadone 5 mg twice a day vs placebo Phase 2: Methadone 10 mg twice a day vs placebo	DB, RCT, XO Patients age 18-80 with a history of more than 3 months of non-malignant neuropathic pain	N=18 40 days (20 days each phase)	Primary: Analgesic effectiveness and adverse events Secondary: Not reported	Primary: Analgesic effects were seen when a daily dose of 10 mg (given as 5 mg twice a day) of methadone was used, but the difference in maximum pain intensity and pain relief did not reach statistical significance (*P*=0.064 and 0.065, respectively). As compared with placebo, the 20 mg daily dose (given as 10 mg twice a day) of methadone resulted in statistically significant (*P*=0.013 to 0.020) improvements for maximum pain intensity, reduction of average pain intensity, and VAS pain relief on the rest days instituted between each daily dose Secondary: Not reported
Ma et al[25] Oxycodone controlled release initial dose of 5-10 mg every 12 hours and increased by 25-50% as needed vs placebo	DB, PRO, RCT Patients age 40-70 with a history of chronic refractory neck pain for over 6 months and MRI or computer topography scan suggesting a degenerative disease process	N=116 4 weeks	Primary: Efficacy measured by frequency of pain flares, VAS, quality of life, and quality of sleep, and adverse effects Secondary: Not reported	Primary: Compared with the pretreatment and placebo group, the frequency of acute pain flares (>3 times/day) in the oxycodone group decreased significantly on day 3 and day 7 (*P*<0.05), only 20.7% of patients (12/58) continued to have acute flare pain >3 times/day on day 7, and 21 days later no patient complained of acute flare pain in the oxycodone group (*P*<0.01) Patients who received oxycodone had a decreased VAS score than the patients in the placebo group (*P*<0.05-0.01). VAS had decreased from 6.82±1.83 to 3.35±1.57 on day 3 and to 3.24± 0.92 on day 7 (*P*<0.05-0.01) in the oxycodone group. Bad quality of sleep was 63.8% before treatment and was decreased to 15.5% on day 3, 8.6% on day 7 and 5.6% on day 14 in patients in the oxycodone group. Additionally, there was significant improvement in the quality of sleep, with 13.8% as the baseline for good quality of sleep, rising to 46.6%, 50.0%, and 58.3% on day 3, 7, and 14

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respectively after oxycodone treatment (*P*<0.01). Side effects, including mild-to-moderate nausea (31.0%) constipation (22.4%), pruritus (18.9%) and dizziness (27.6%) were only seen on day 7 of the treatment in oxycodone patients (*P*<0.05). However, these side effects diminished starting from day 14 of the treatment until day 28; only 2 patients had persistent constipation. Secondary: Not reported
Bruera et al[26] Oxycodone controlled release every 12 hours for 7 days vs morphine controlled release every 12 hours for 7 days	DB, RCT, XO Patients 18 years of age or older, with cancer pain and at least a 3 day history of stable analgesia with oral opioids	N=32 2 weeks	Primary: Pain intensity and adverse events Secondary: Not reported	Primary: There were no significant differences between treatments in pain-intensity VAS scores when tested by day of treatment, time of day, or overall (*P*=0.43) or between categorical scale pain-intensity scores by day of treatment, time of day, or overall (*P*=0.36). The mean dose of oxycodone controlled release was 46.5±57.0 mg every 12 hours vs 72.6±102.0 mg every 12 hours for morphine controlled release. For both formulations, there was a significant (*P*=0.02) difference in rescue use with respect to doses taken during the night (2am to 6am) as compared with the remainder of the 24-hour day. The rate of rescue use during the night was 55% and 67% of that used during the daytime in the controlled-release oxycodone and controlled-release morphine groups, respectively. The average daily number of rescue doses in a 24-hour period was 2.3±2.3 for oxycodone controlled release and 1.7±2.1 for morphine controlled release (*P*=0.01). There were no significant differences in sedation or nausea between controlled-release oxycodone and controlled-release morphine. Secondary: Not reported
Caldwell et al[27] Morphine extended release (Avinza®)	DB, DD, MC, PC, RCT Patients at least	N=295 4 weeks	Primary: Efficacy and safety of Avinza® compared to	Primary: Overall, a statistically significant reduction in pain from baseline was demonstrated by Avinza® in the morning (17%) and in the evening (20%), and MS Contin® twice daily (18%), as compared to placebo (4%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
30 mg plus placebo in the morning and 2 placebos at night vs 2 placebos in the morning and morphine extended release (Avinza®) plus placebo at night vs morphine controlled release (MS Contin®) 15 mg in the morning plus placebo with same regimen at night vs 2 placebos in the morning and 2 placebos at night	40 years of age and had a clinical diagnosis and grade II-IV radiographic evidence of OA of the hip and or knee and had suboptimal analgesic response to treatment with NSAIDS and acetaminophen		placebo MS Contin® Secondary: Comparison of the analgesic efficacy of Avinza® and MS Contin	Avinza® in the morning (26%) and in the evening (22%), and MS Contin® twice daily (22%) reduced overall arthritis pain intensity as compared with placebo (14%), but these differences were not statistically significant. Statistically significant differences in physical function were not achieved among the treatment groups. Active treatment groups provided greater improvements in all sleep measures vs placebo. Avinza® in the morning provided a statistically significant improvement vs placebo for overall quality of sleep, less need for sleep medication, increases hours of sleep, and less trouble falling asleep because of pain. Patients receiving Avinza® in the evening demonstrated a statistically significant improvement in overall quality of sleep compared to MS Contin® for weeks 1 and 4 ($P \leq 0.05$). No statistical differences were observed between Avinza® in the morning and in the evening. A total of 197 patients (67%) experienced at least one adverse event during this trial. Constipation and nausea were reported most frequently. Adverse events were higher in all active treatment groups than in the placebo group. Among the 33 pair-wise comparisons the only significant differences observed were a higher rate of constipation with Avinza® in the morning (49%) vs MS Contin® (29%), a higher rate of vomiting with Avinza® in the evening (16%) vs Avinza® in the morning (6%), and a higher rate of asthenia with MS Contin® (9%) vs Avinza® in the morning (1%).

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, DR=dose-ranging, INT=international, MC=multicenter, MD=multi-dose, OL=open label PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SA=single arm, SD=standard deviation, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, $AUCMB_{avg}$=average AUC of VAS scores overtime between baseline and end of study, BDI=Beck depression inventory, EORTC=European Organization for Research and Treatment of Cancer, ITT=intention to treat, MPI=multidimensional pain inventory, MRI=magnetic resonance imaging, NSAIDS=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, SEM=standard error of the mean, SF-36=short form 36 health assessment questionnaire, TDF=transdermal fentanyl, VAS=visual analog scale, WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index

Special Populations

Table 5. Special Populations[4-12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Fentanyl	Use with caution in elderly. Safety has not been evaluated in children less than 2 years of age.	If a glomerular filtration rate of 10-50 mL/minute, 75% of the normal dose should be administered and 50% of the dose should be administered if the glomerular filtration rate is <10 mL/minute.	Lower doses are suggested in the presence of chronic liver disease.	C	Yes (% not reported)
Methadone	Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	The use of methadone has not been extensively evaluated in patients with renal insufficiency.	The use of methadone has not been extensively evaluated in patients with hepatic insufficiency.	C	Yes (2%-3%)
Morphine Sulfate	Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	If a glomerular filtration rate of 10-50 mL/minute, 75% of the normal dose should be administered and 50% of the dose should be administered if the glomerular filtration rate is <10 mL/minute.	The duration of action of morphine is prolonged in patients with hepatic insufficiency; dosages should be adjusted.	C	Yes (% not reported)

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Oxycodone	Clearance may be slightly reduced in elderly. Safety and effectiveness have not been established in pediatric patients below the age of 18.	Increased risk of toxicity in severe renal impairment. Dose initiation should follow a conservative approach.	The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.	B	Yes (% not reported)
Oxymorphone	Use caution in elderly patients. The plasma levels of oxymorphone are about 40% higher in elderly (≥ 65 years of age) than in younger subjects. Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	Patients with moderate to severe renal impairment were shown to have an increase in bioavailability ranging from 57-65%. Patients with moderate to severe renal impairment should be started cautiously with lower doses and titrated slowly while carefully monitored for side effects.	Caution should be used in patients with mild impairment. These patients should be started with the lowest dose and titrated slowly while carefully monitoring for side effects. Contraindicated for patients with moderate and severe hepatic impairment.	C	Unknown

Adverse Drug Events[4-12]

The adverse drug events for the long acting narcotics are similar to each other and represent the pharmacologic effects of the drug class. The most serious and most feared opioid-induced adverse reaction is respiratory depression. Patients receiving opioids chronically rarely experience this effect since tolerance to respiratory depression develops.

The most frequently observed adverse effects include nausea and vomiting, sedation, constipation, dizziness, and lightheadedness. These adverse effects typically occur early in therapy or immediately after a dosage increase. Over time these adverse events tend to subside as tolerance develops. However, constipation is the one exception, as unlike other opioid-induced adverse effects, tolerance to constipation does not develop.

Other adverse drug events commonly seen with the long acting narcotics are:

Cardiovascular System: bradycardia, chills, faintness, flushing of the face, hypertension, hypotension, palpitations, syncope, vasodilatation

Central Nervous System: abnormal dreams, agitation, amnesia, confusion, convulsions, delirium, depression, disorientation, dreams, dysphoria, euphoria, headache, insomnia,

muscle rigidity, nervousness, transient hallucinations, tremor, uncoordinated muscle movements, visual disturbances, and weakness
Dermatologic: dry skin, edema, hemorrhagic urticaria, pruritus, rash, sweating, urticaria
Gastrointestinal: abdominal pain, anorexia, biliary tract spasm, dry mouth, taste alterations
Genitourinary System: amenorrhea, anti-diuretic effect, reduced libido and/or potency, urinary retention
Respiratory System: bronchospasm, hypoventilation, voice alteration

Contraindications / Precautions[4-12]
The long acting narcotics should not be administered to patients with known hypersensitivity to any component of the product.

Long acting narcotics are contraindicated in patients with significant respiratory depression. They should be used in caution in patients with acute asthma, chronic obstructive pulmonary disorder, or preexisting respiratory impairment. Additionally, the respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid may be markedly exaggerated in the presence of head injury, intracranial lesions, or a pre-existing increase in intracranial pressure.

Opioid analgesics may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone.

Long acting narcotics should not be administered to patients with gastrointestinal obstruction, especially paralytic ileus.

All of the agents in this class have black box warnings associated with them. These black box warnings are listed below:

Black Box Warning for Avinza® (morphine sulfate extended release)[8]

WARNING
WARNING: AVINZA® capsules are a modified-release formulation of morphine sulfate indicated for once daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. AVINZA® CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLESAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE. PATIENTS MUST NOT CONSUME ALCOHOLIC BEVERAGES WHILE ON AVINZA THERAPY. ADDITIONALLY, PATIENTS MUST NOT USE PRESCRIPTION OR NON-PRESCRIPTION MEDICATIONS CONTAINING ALCOHOL WHILE ON AVINZA THERAPY. CONSUMPTION OF ALCOHOL WHILE TAKING AVINZA® MAY RESULT IN THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

Black Box Warning for Kadian® (morphine sulfate extended release)[9]

WARNING
WARNING: KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is

WARNING
needed for an extended period of time. KADIAN® Capsules are NOT for use as an as needed analgesic. KADIAN® 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN® CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE PELLETS IN THE CAPSULES ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

Black Box Warning for MS Contin® (morphine sulfate controlled release)[7]

WARNING
WARNING: MS CONTIN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing MS CONTIN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. MS CONTIN® tablets are a controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the- clock opioid analgesic is needed for an extended period of time. MS CONTIN® tablets are NOT intended for use as an as needed analgesic. MS CONTIN® 100 and 200 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids. MS CONTIN® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, DISSOLVED, OR CRUSHED. TAKING BROKEN, CHEWED, DISSOLVED, OR CRUSHED MS CONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

Black Box Warning for Oxycontin® (oxycodone controlled release)[11]

WARNING
WARNING: OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. OxyContin® tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin® tablets are NOT intended for use as an as needed analgesic. OxyContin® 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids. OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Black Box Warning for Opana ER® (oxymorphone extended release)[12]

WARNING
WARNING: OPANA ER® contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. OPANA ER® is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. OPANA ER® is NOT intended for use as an as needed analgesic. OPANA ER® TABLETS are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA ER® TABLETS leads to rapid release and absorption of a potentially fatal dose of oxymorphone. Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER® therapy. The co-ingestion of alcohol with OPANA ER® may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Black Box Warning for Duragesic® (fentanyl transdermal patch)[5]

WARNING
DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion. DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that: • requires continuous, around-the-clock opioid administration for an extended period of time, and • cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid. Because serious or life-threatening hypoventilation could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated: • in patients who are not opioid-tolerant • in the management of acute pain or in patients who require opioid analgesia for a short period of time • in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies) • in the management of mild pain • in the management of intermittent pain [e.g., use on an as needed basis] (See CONTRAINDICATIONS for further information.) Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid tolerant patients, during the initial application period. The concomitant use of DURAGESIC® with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone,

WARNING
amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving DURAGESIC® and any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted The safety of DURAGESIC® has not been established in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS - Pediatric Use). DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of DURAGESIC®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours. DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing DURAGESIC® in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction. DURAGESIC® patches are intended for transdermal use (on intact skin) only. Do not use a DURAGESIC® patch if the seal is broken or the patch is cut, damaged, or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal. Avoid exposing the DURAGESIC® application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, while wearing the system. Avoid taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. Patients wearing DURAGESIC® systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.

Black Box Warning for Methadone[6]

WARNING
Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred because of the respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration. Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment. Respiratory depression is the chief hazard associated with methadone administration. Methadone's peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to the cases of iatrogenic overdose, particularly during treatment initiation and dose titration. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed

WARNING

during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Conditions for distribution and use of methadone products for the treatment of opioid addiction:
Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners, or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See the following information for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Regulatory exceptions to the general requirement for certification to provide opioid agonist treatment include the following:

- During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07[c]), to facilitate the treatment of the primary admitting diagnosis.
- During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07[b])

Drug Interactions

Table 6: Drug Interactions[4-12]

Generic Name	Interacting Medication or Disease	Potential Result
Morphine Oxycodone Oxymorphone Fentanyl Methadone	Mixed agonist/ antagonist opioid analgesics	Mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.
Morphine Oxycodone Oxymorphone Fentanyl	Central nervous system depressants	The concurrent use of other central nervous system depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, or other tranquilizers or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma.
Morphine Oxycodone Oxymorphone Fentanyl	Muscle relaxants	Concomitant administration may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Fentanyl Methadone Oxycodone	Cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, erythromycin,	Concomitant administration may result in an increase in narcotic plasma concentrations, which could increase or prolong adverse drug effects and may cause fatal respiratory depression.

Generic Name	Interacting Medication or Disease	Potential Result
	nefazodone, verapamil, grapefruit juice)	
Morphine Fentanyl Methadone	Monoamine oxidase inhibitors (MAOIs)	MAOIs markedly potentiate the action of narcotics.
Morphine Oxymorphone	Cimetidine	Concomitant administration has been reported to precipitate apnea, confusion, and muscle twitching.
Methadone	Agents that affect QT interval (amiodarone, levofloxacine, quinidine, sotalol, ziprasidone)	Concomitant administration may result in QT interval prolongation and serious arrhythmia (torsades de pointes).
Methadone	Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir/ritonavir	Concomitant administration may result in increased clearance or decreased plasma levels of methadone.
Methadone	Desipramine	Concomitant administration may result in increased levels of desipramine.
Methadone	Didanosine, stavudine	Methadone may decrease the area under the curve and peak levels for didanosine and stavudine.
Methadone	Zidovudine	Methadone increased the area under the concentration-time curve of zidovudine which could result in toxic effects.
Morphine	Diuretics	Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Morphine	Metformin	Concurrent use may result in increased metformin plasma concentrations.
Morphine	Rifampin	Concurrent use of morphine and rifampin may result in loss of morphine efficacy.
Oxymorphone	Anticholinergics	Concomitant administration may result in an increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Oxycodone	Selective serotonin reuptake inhibitors	Concurrent use may result in an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes).

Dosage and Administration

Table 7. Dosing and Administration[4-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Fentanyl	Management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such	Management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be	Transdermal patch: 12 µg/hour 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour

Generic Name	Adult Dose	Pediatric Dose	Availability
	as non-steroidal analgesics, opioid combination products, or immediate release opioids: Transdermal patch: dose is highly variable and based on calculated equianalgesic dose of oral morphine	managed by other means such as non-steroidal analgesics, opioid combination products, or immediate release opioids: Transdermal patch: dose is highly variable and based on calculated equianalgesic dose of oral morphine	
Methadone	Treatment of moderate to severe pain not responsive to non-narcotic analgesics: Tablet: 2.5-10 mg every 8-12 hours Detoxification treatment of opioid addiction: Tablet: initial, 15-30 mg; maintenance, 40 mg per day in single or divided doses A detoxification treatment course should not exceed 21 days and may not be repeated earlier than 4 weeks after completion of the preceding course. Maintenance treatment of opioid addiction, in conjunction with appropriate social and medical services: Tablet: maintenance, 80-120 mg per day	Safety and effectiveness in pediatric patients below the age of 18 years have not been established	Tablet: 5 mg 10 mg 40 mg (detox, maintenance only – not for pain)
Morphine	Management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time: Controlled-release tablet: initial, conversion to controlled release morphine can be administered at one-half of the estimated total daily morphine requirement once every 12 hours or at one-third of the total daily requirement every 8 hours The 100 and 200 mg controlled-release tablets are intended for use in opioid-tolerant patients requiring daily morphine	Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	Controlled-release tablet: 15 mg 30 mg 60 mg 100 mg 200 mg Extended-release capsules (Avinza®): 30 mg 45 mg 60 mg 75 mg 90 mg 120 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	equivalent dosages of 200 mg or more Relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time: Extended-release capsule (Avinza®): initial, 30 mg every 24 hours; maintenance, dosage adjustments of not greater than 30 mg every 4 days; maximum, 1,600 mg per day Extended-release capsule (Kadian®): initial, 20 mg per day administered in once or twice a day dosing; maintenance, dosage may be adjusted at a 20 mg increment no more frequently than every-other-day Relief of pain in patients who require opioid analgesics for more than a few days: Sustained-release tablet: initial, 30 mg every 8 hours, may administer one-third of the patients daily morphine requirement every 8 hours or one-half the required dose every 12 hours		Extended-release capsule (Kadian®): 10 mg 20 mg 30 mg 50 mg 60 mg 80 mg 100 mg 200 mg Sustained-release tablet: 15 mg 30 mg 60 mg 100 mg
Oxycodone	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time: Controlled-release tablet: initial, 10 mg every 12 hours; maintenance, 60-160 mg every 12 hours; maximum; 80 mg per day with a single maximum dose of 40 mg Adjustments may be made every 1-2 days; dosage strengths should be adjusted rather than dosage frequency; total daily dose can usually be increased 25-50% of current dose at each increase titrate up to 40 mg every 12 hours as necessary.	Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	Controlled-release tablet: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg 80 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Oxymorphone	Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time: Tablet: initial, 5 mg every 12 hours; maintenance, titrate at increments of 5-10 mg every 12 hours every 3-7 days	Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	Tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg

Other Key Facts

During the course of pain management the process of converting from one opioid to an equivalent dose of another, or changing the route of administration, can be done using morphine as a reference. The following eight steps can be utilized when a change is appropriate: [28]

Step 1: Determine the total 24-hour dose of the currently prescribed analgesic.
Step 2: Convert the currently prescribed opioid to the equivalent morphine dose.
Step 3: Convert the morphine dose to an equivalent dose of the new opioid using the same route of administration using the following conversions:

- Consider reducing the dose by 50% in the elderly and patients with renal failure.
- When changing the route of administration, it is suggested that the morphine equianalgesic dose first be determined prior to calculating the new dose (oral to intravenous morphine conversion is 3:1, oral to subcutaneous morphine conversion is 2:1).

Step 4: If pain is controlled, start at 50-75% of the equianalgesic dose; if the pain is uncontrolled than start at 100% of the dose.
Step 5: Determine the appropriate intervals of administration and amount per dose.
Step 6: Provide appropriate rescue dosing for breakthrough pain.
Step 7: Titrate baseline and as needed doses to provide effective pain relief.
Step 8: Cathartic and stool-softening medications should be started with the initiation of opioids.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction[6] (Code of Federal Regulations, Title 42, Sec 8):

- Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12).
- Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
American Pain Society: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[29]	• Before initiating chronic opioid therapy, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction. • When starting chronic opioid therapy, informed consent should be obtained. A continuing discussion with the patient regarding chronic opioid therapy should include goals, expectations, potential risks, and

Clinical Guideline	Recommendations
	alternatives to chronic opioid therapy. • Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. • In patients on chronic opioid therapy who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. • Clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist. • In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the treatment plan on an ongoing basis, and consider more frequent follow-up visits. • Clinicians should taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects. • In patients on around-the-clock chronic opioid therapy with breakthrough pain, clinicians may consider as needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk. • Clinicians should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Clinicians should encourage minimal or no use of opioids during pregnancy, unless potential benefits outweigh risks. If chronic opioid therapy is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn.
American College of Rheumatology Subcommittee on Osteoarthritis: **Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee (2000)**[30]	• The goals of management of patients with osteoarthritis include control of pain and improvement in function and health-related quality of life, with avoidance of toxic effects of therapy. • Drug therapy for pain management is most effective when combined with nonpharmacologic strategies, therefore nonpharmalogical therapies should be maintained throughout treatment. <u>Nonpharmacological Therapy</u> • Patient and family/caregiver education, participation in self-management programs and personalized social support are recommended to improve outcomes. • Physical therapy and occupational therapy play central roles in the management of patients with functional limitations. • Quadricep strengthening and aerobic exercise are recommended for patients with knee osteoarthritis. • Weight loss is recommended in patients with knee and hip osteoarthritis. • Assistive devices for ambulation, patellar taping, appropriate footwear, bracing and assistive devices may help improve mobility and activities of daily living.

Clinical Guideline	Recommendations
	Pharmacological Therapy • Relief of mild-to-moderate joint pain afforded by the simple analgesic, acetaminophen (APAP), is comparable with that achievable with a nonsteroidal anti-inflammatory drugs (NSAIDs). • In individuals with osteoarthritis of the knee who have mild-to-moderate pain, do not respond to APAP, and do not wish to take systemic therapy, the use of topical analgesics (e.g., methyl salicylate or capsaicin cream) is appropriate as either adjunctive treatment or monotherapy. • The options for medical management of osteoarthritis that has not responded to APAP or topical agents in patients who are at increased risk for a serious upper gastrointestinal adverse event, such as bleeding, perforation, or obstruction, include cyclooxygenase (COX)-2 inhibitors, a nonselective NSAID plus misoprostol or a proton pump inhibitor, non-acetylated salicylate , or local intraarticular therapy. • Celecoxib has been found to be more effective than placebo and comparable in efficacy with naproxen in patients with hip or knee osteoarthritis. • Of further advantage with respect to upper gastrointestinal bleeding, neither of the COX-2-specific inhibitors has a clinically significant effect on platelet aggregation nor bleeding time. • Coxibs are an alternative to nonselective NSAIDs in patients at risk of developing gastrointestinal toxicity associated with NSAID therapy. • Additionally, at doses recommended for treatment of osteoarthritis, both celecoxib and rofecoxib appear to be better tolerated, with a lower incidence of dyspepsia and other gastrointestinal side effects, than comparator nonselective NSAIDs. • Tramadol, a centrally acting opioid agonist, can be considered for use in patients who have contraindications to COX-2-specific inhibitors and nonselective NSAIDs, including impaired renal function or in patients who have not responded to previous oral therapy. • More potent opioid therapy can be considered in patients who do not respond to or cannot tolerate tramadol and who continue to have severe pain. • It is reasonable to use the recommended agents in combination. However, only a single NSAID should be used at any given time, the sole exception being the concomitant use of a cardioprotective dose of aspirin (81-325 mg/day) with other NSAIDs.
American Academy of Orthopedic Surgeons (AAOS): **Clinical Practice Guideline on Osteoarthritis of the Knee (2008)**[31]	Nonpharmacological/Surgical Therapy • Patients with symptomatic osteoarthritis of the knee should be encouraged to participate in self-management educational programs, lose and maintain weight loss if overweight (body mass index >25), participate in low-impact aerobic fitness exercises and use range of motion/flexibility exercises and quadriceps strengthening. • Patients with symptomatic osteoarthritis of the knee should use patellar taping for short term relief of pain and improvement in function. Lateral heel wedges should not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee. • Needle lavage and arthroscopy with debridement or lavage should not be used for patients with primary symptomatic osteoarthritis of the knee. Arthroscopic partial meniscectomy or loose body removal is an option in patients with symptomatic osteoarthritis of the knee who also have primary signs and symptoms of a torn meniscus and/or a loose

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>body.

Pharmacological Therapy
• Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee.
• Patients with symptomatic osteoarthritis of the knee should receive one of the following analgesics for pain unless there are contraindications to this treatment:
  ○ APAP (not to exceed 4 grams per day)
  ○ NSAIDs
• Patients with symptomatic osteoarthritis of the knee and increased gastrointestinal risk (age ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of gastrointestinal bleeding, concurrent corticosteroids and/or concomitant use of anticoagulants) should receive one of the following analgesics for pain:
  ○ APAP (not to exceed 4 grams per day)
  ○ Topical NSAIDs
  ○ Nonselective oral NSAIDs plus gastro-protective agent
  ○ COX-2 inhibitors
• Intra-articular corticosteroids can be used for short-term pain relief for patients with symptomatic osteoarthritis of the knee.</td></tr>
<tr><td>Treatment Guidelines from The Medical Letter: Drugs for Pain (2007)[32]</td><td>• Aspirin, APAP, and NSAIDS are recommended as first line agents for mild to moderate pain.
• For moderate pain, NSAIDS have been shown to be more effective than aspirin and APAP, and may be equal to or greater than APAP/opioid combination products or opioids administered via injection, at recommended doses.
• Strong opioid full agonists are recommended as the first line treatment for severe pain.
• Full opioid agonists generally have no ceiling effect and the dose may be increased as tolerated based on adverse effects.
• Patients who do not respond to one opioid may respond to another. The choice of opioid should be based on adequate analgesia being provided with minimal adverse effects.
• When frequent as-needed dosing with short–acting agents becomes inappropriate, use of long-acting agents is warranted.
• Combination regimens, including opioids, non-opioids, and adjuvant analgesics, are useful for severe chronic pain.</td></tr>
<tr><td>American College of Physicians (ACP): Guidelines for the Diagnosis and Treatment of Low Back Pain (LBP) (2007)[33]</td><td>• Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work), and duration of symptoms.
• The potential interventions for lower back pain are outlined below:
Interventions for the Management of LBP
<table><tr><th>Intervention type</th><th>Acute pain (duration < 4 weeks)</th><th>Subacute or chronic pain (duration > 4 weeks)</th></tr><tr><td>Self-care</td><td></td><td></td></tr><tr><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr><tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr><tr><td>Books, handouts</td><td>Yes</td><td>Yes</td></tr><tr><td>Pharmacologic therapy</td><td></td><td></td></tr></table></td></tr>
</table>

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td>APAP</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Tricyclic antidepressants</td><td>No</td><td>Yes</td></tr>
<tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr>
<tr><td>NSAIDs</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Yes</td><td>No</td></tr>
<tr><td>Tramadol, opioids</td><td>Yes</td><td>Yes</td></tr>
<tr><td colspan="3">Nonpharmacologic therapy</td></tr>
<tr><td>Acupuncture</td><td>No</td><td>Yes</td></tr>
<tr><td>Cognitive behavior therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Exercise therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Massage</td><td>No</td><td>Yes</td></tr>
<tr><td>Progressive relaxation</td><td>No</td><td>Yes</td></tr>
<tr><td>Spinal manipulation</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Yoga</td><td>No</td><td>Yes</td></tr>
<tr><td>Intensive interdisciplinary rehabilitation</td><td>No</td><td>Yes</td></tr>
</table>
Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

• Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
• In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, APAP or NSAIDs are the first-line options.
• APAP is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
• Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with APAP or NSAIDs. Evidence is insufficient to recommend one opioid over another.</td></tr>
<tr><td>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: Diagnosis and Treatment of LBP</td><td>• Clinicians should consider the use of medications with proven benefits in conjunction with self-care.
• Clinicians should assess the severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy.
• For most patients, first-line medical options are APAP or NSAIDs.</td></tr>
</table>

Clinical Guideline	Recommendations
(2007)[34]	• Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution. • Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
British Society for Rheumatology and British Health Professionals in Rheumatology: **Guideline for the Management of Gout (2007)**[35]	Management of Acute Gout • After an acute gout episode, affected joints should be rested and analgesic and anti-inflammatory drug therapy should be commenced immediately and continued for 1 to 2 weeks. • Fast-acting oral NSAIDs at maximum doses are the drugs of choice in gout when there are no contraindications. • Physicians should follow standard guidelines for the use of NSAIDs and COX-2 inhibitors in patients with increased risk of peptic ulcers, bleeds or perforations. • Colchicine can be an effective alternative but it has a slower onset of action than NSAID therapy. • Allopurinol should not be commenced during an acute attack. It should be continued if used when an acute attack occurs and the acute attack should be treated conventionally. • Opiate analgesics can be used as adjunct therapy. • Intra-articular corticosteroids are highly effective in acute gouty mono-arthritis and can be effective in patients unable to tolerate NSAIDs or in patient's refractory to other treatments. Diet, Lifestyle Modification and Non-pharmacological Therapy • In overweight patients, dietary modification should be attempted to achieve ideal body weight. However, "crash dieting" and high protein/low carbohydrate diets should be avoided. Patients should be instructed on proper diet to avoid precipitation of an acute gout attack. • Affected joints should be elevated and exposed in a cool environment. • Moderate physical exercise should be encouraged. Management of Recurrent, Intercritical and Chronic Gout • The plasma urate should be maintained below 300 µmol/L. • Uric acid lowering drug therapy should be started if further attacks occur within 1 year and should also be offered to patients with tophi, renal insufficiency, uric acid stones and to patients who need to continue treatment with diuretics. • Uric acid-lowering drug therapy should be delayed until 1 to 2 weeks after inflammation has settled. • Long-term treatment of recurrent uncomplicated gout should be initiated with allopurinol at a starting dose of 50 to 100 mg daily and increasing by 50 to 100 mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (plasma urate <300 µmol/L) or maximum dose (900 mg daily) is reached. • Uricosuric agents can be used as second-line drugs in patients who excrete sufficient uric acid in those resistant to, or intolerant of, allopurinol. Preferred drugs include: sulphinpyrazone in patients with normal renal function or benzbromarone in patients with mild to

Clinical Guideline	Recommendations
	moderate renal insufficiency. • Colchicine should be co-prescribed following initiation of treatment with allopurinol or uricosuric drugs, and continued for up to 6 months. An NSAID or COX-2 inhibitor can be substituted if colchicine cannot be used (provided that there are no contraindications). However, the duration of therapy should be limited to 6 weeks. • Aspirin in low doses (75 to 150 mg daily) has insignificant effects on the plasma urate and can be used; however, aspirin in analgesic doses (600 to 2,400 mg daily) interferes with uric acid excretion and should be avoided.
American Society of Pain Educators: **Treatment Guidelines for Diabetic Peripheral Neuropathic Pain (2006)**[36]	• For the treatment of diabetic peripheral neuropathic pain, first line agents, including duloxetine, controlled release oxycodone, pregabalin, and tri-cyclic antidepressants (TCAs), should be titrated to maximum tolerated doses. • If no improvement is seen within 3 weeks of initiating therapy, second line agents may be considered (carbamazepine, gabapentin, lamotrigine, tramadol, and extended release venlafaxine). • Other recommended agents include topical capsaicin, topical lidocaine, bupropion, citalopram, methadone, paroxetine, phenytoin, and topiramate.
European Federation of Neurological Societies: **Guidelines on Pharmacological Treatment of Neuropathic Pain (2006)**[37]	<u>Painful Polyneuropathy</u> • Treatments with established efficacy include TCAs, duloxetine, venlafaxine, gabapentin, pregabalin, opioids and tramadol. • A TCA, gabapentin or pregabalin are considered first line agents. • Duloxetine and venlafaxine are considered second line agents. • Duloxetine and venlafaxine have moderate efficacy, but are safer and have less contraindications than TCAs and should be preferred to TCAs in patients with cardiovascular risk factors. • Other second/third-line agents include opioids and lamotrigine. <u>Postherpetic Neuralgia</u> • Treatments with established efficacy include TCAs, gabapentin, pregabalin and opioids. • A TCA, gabapentin or pregabalin are considered first line agents. • Topical lidocaine may be an option in elderly patients, particularly in patients with allodynia and a small area of pain. • Opioids should be considered a second line agent. <u>Trigeminal Neuralgia</u> • Carbamazepine and oxcarbazepine are considered first line agents. • There is no evidence that combination therapies are advantageous. <u>Central Pain</u> • Treatment may be based on general principles for peripheral neuropathic pain treatment and for side-effect profile. • A trial with other drugs found effective on other central pain conditions is the recommended treatment.
Canadian Pain Society: **Pharmacological Management of Chronic Neuropathic Pain- Consensus**	• First-line treatments consist of certain antidepressants (TCAs) and anticonvulsants (gabapentin and pregabalin). • Second-line treatments consist of serotonin/noradrenaline reuptake inhibitors and topical lidocaine. • Third-line treatments consist of tramadol and controlled-release opioids.

Clinical Guideline	Recommendations
Statement and Guidelines (2007)[38]	• Fourth-line treatments consist of cannabinoids, methadone and anticonvulsants with lesser evidence of efficacy, such as lamotrigine, topiramate and valproic acid. • Treatment must be individualized for each patient based on efficacy, side-effect profile and drug accessibility, which includes cost.
European League Against Rheumatism: **Evidence-Based Recommendations for the Management of Fibromyalgia Syndrome (2008)**[39]	• Tramadol is recommended for the management of pain in fibromyalgia. • Simple analgesics such as APAP and other weak opioids can be considered in the treatment of fibromyalgia. Corticosteroids and strong opioids are not recommended. • Antidepressants such as amitriptyline, fluoxetine, duloxetine and pregabalin reduce pain and should be considered for the treatment of fibromyalgia.

Conclusions

Opioids (narcotics) have been the mainstay of pain treatment for a number of years with long acting narcotic agents playing an important role in the treatment of moderate to severe chronic pain. Clinical trials have shown their efficacy in treating pain due to a number of etiologies. Despite numerous head to head trials with long acting agents, no one agent has continuously proven to be more effective than another when given at equipotent doses.

The long acting narcotics are similar in their documented adverse events as the adverse events tend to be class effects rather than effects of a specific agent. Many of these adverse effects subside with continued dosing as tolerance is built.

Recommendations

In recognition of the well established role of long-acting narcotics in the management of chronic pain and the availability of many oral generics, it is recommended that morphine sulfate SR 12 hr and methadone are preferred oral products available without prior authorization. Duragesic patches are the preferred transdermal formulation.

CRITERIA FOR APPROVAL (NON-PREFERRED):

Transdermal: (generic fentanyl patches)

- The patient has a diagnosis or condition that requires a continuous, around-the-clock analgesic.

AND

- The patient has had a documented intolerance to brand name Duragesic.

Duragesic-12 will be approved for patients who are titrating from one strength to another and the available strengths of Duragesic are not appropriate. Duragesic-12 is not indicated for initial dosing. For approval of Fentanyl 12.5 mcg/hr, the patient must have had a documented intolerance to Duragesic-12.

Oral Non-Preferred:

- The patient has a diagnosis or condition that requires a continuous, around-the-clock analgesic.

AND

- The patient has had a documented side effect, allergy, or treatment failure to morphine sulfate SR 12 hr (If a product has an AB rated generic, there must have been a trial of the generic).

References:

1. International Association for the Study of Pain. IASP Pain Terminology. Accessed December 29, 2008 at http://www.iasp-pain.org/terms-p.html#Pain.
2. American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 5th ed. American Pain Society, Glenview, IL, 2003.
3. Federation of State Medical Boards. Model guidelines for the use of controlled substances for the treatment of pain. Accessed 2009 February 6 at http://www.painpolicy.wisc.edu/domestic/model.htm.
4. Micromedex® Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Micromedex; 2009 [cited 2009 Jan 20]. Available from http://www.thomasonhc.com/.
5. Duragesic® (fentanyl transdermal system) [package insert]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2008 Feb.
6. Dolopine® (methadone Hydrochloride Tablets) [package insert]. Columbus, OH: Roxane Laboratories, Inc.; 2006 Oct.
7. MS Contin® (morphine sulfate controlled-release tablets) [package insert]. Stamford, CT: Purdue Pharma L.P.; 2007 Aug.
8. Avinza® (morphine sulfate extended-release capsules) [package insert]. Bristol, TN: King Pharmaceuticals, Inc.; 2008 April.
9. Kadian® (morphine sulfate extended-release capsules) [package insert]. Piscataway, NJ: Alpharma Pharmaceuticals LLC; 2008 Jan.
10. Oramorph® SR (morphine sulfate sustained release tablets) [package insert]. Newport, KY: Xanodyne Pharmaceuticals, Inc.; 2006 Feb.
11. Oxycontin® (oxycodone HCL controlled-release tablets) [package insert]. Stamford, CT: Purdue Pharma L.P.; 2007 Nov.
12. Opana® ER (oxymorphone hydrochloride extended-release tablets) [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc.; 2008 Feb.
13. Jovey RD, Ennis J, Gardner-Nix J, et al. Use of opioid analgesics for the treatment of chronic non-cancer pain. A consensus statement and guidelines from the Canadian pain society 2002. *Pain Res Manag*. 2003; 8(Suppl A):3A-14A.
14. Furlan AD, Sandoval JA, Mailis-Gagnon AC, Tunks E. Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006; 174(II):1589-94.
15. Langford R., McKenna F., Ratcliffe S., Vojtassak J., Richarz U. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. *Arthritis & Rheumatism* 2006; 54(6):1829-37.
16. Finkel JC., Finley A., Greco C., Weisman SJ., Zeltzer L. Transdermal fentanyl in the management of children with chronic severe pain. Results from an international study. *Cancer*. 2005; 104:2847-57.
17. Allan L. Hays H. et al. Randomized crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ*. 2001; 322:1-7.
18. Agarwal A., Polydefkis M., Block B., Haythornthwaite J., Raja S. Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. *Pain Medicine*. 2007; 8(7):554-62.
19. Ahmedzai S., Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain; preference, efficacy, and quality of life. *J Pain Symptom Manage*. 1997; 13:254-61.
20. Allan L., Richarz U., Simpson K., Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. *Spine.* 2005; 30(22):2484-90.
21. Sloan P., Slatkin N., Ahdieh H. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. *Support Care Cancer.* 2005; 13:57-65.
22. Kivitz A., Ma C., Ahdieh H., Galer BS. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clinical Therapeutics.* 2006; 38(3):352-64.

23. Bruera E. et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol*. 2004; 22(1):185-92.
24. Morley JS., Bridson J., Nash TP., Miles JB., White S., Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliative Medicine.* 2003; 17:576-87.
25. Ma K., Jiang W., Zhou Q., Du DP. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. *Int J Clin Pract.* 2008; 62(2):241-7.
26. Bruera E. et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *Journal of Clinical Oncology.* 1998; 16:3222-9.
27. Caldwell JR et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open label extension trial. *J Pain Symptom Manage*. 2002; 23:278-91.
28. Schneider C, Yale SH, Larson M. Principles of pain management. Outpatient practice management tips. Clinical Medicine & Research. 2003; 1(4):337-40.
29. Chou R, et al. American Pain Society: Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. The Journal of Pain. 2009; 10(2):113-30.
30. American College of Rheumatology Subcommittee on Osteoarthritis: Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum. 2000 Sep;43(9):1905-15.
31. American Academy of Orthopedic Surgeons (AAOS): Clinical practice guideline on the treatment of osteoarthritis of the knee (non-arthroplasty). Rosemont (IL): 2008 [Guideline on the internet] [cited 2009 Jan 21] Available from: http://www.aaos.org/research/guidelines/OAKguideline.pdf.
32. Medical Letter, Inc. Treatment guidelines from the Medical Letter: Drugs for Pain. 2007;5(56):23-32.
33. American College of Physicians (ACP): Guidelines for the diagnosis and treatment of low back pain. [Guideline on the internet]. [Cited 2009 Jan 28]. Available from: www/annals.org/cgi/content/full/147/7/478. 2007.
34. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Int Med. 2007 Oct 2;147(7):478-91.
35. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology. Guideline for the management of gout. Rheumatology (Oxford). 2007 Aug;46(8):1372-4.
36. Argoff CE, et al. Consensus guidelines: Treatment planning and options. Mayo Clin Proc. 2006;81(4, suppl):S12-S25.
37. Attal N, Cruccu G, Haanpaa M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J of Neuro 2006; 13:1153-69.
38. Moulin DE, et al. Pharmacological management of chronic neuropathic pain- Consensus statement and guidelines from the Canadian pain society. J. Pain Res. Manage. 2007;12:13-21.
39. Carville SF. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis. 2008; 67:536-41.